

(19)



Europäisches Patentamt  
European Patent Office  
Office européen des brevets



(11) Publication number:

**0 491 415 A1**

(12)

**EUROPEAN PATENT APPLICATION**(21) Application number: **91203182.0**(51) Int. Cl.<sup>5</sup>: **A61K 31/565**(22) Date of filing: **05.12.91**(30) Priority: **13.12.90 EP 90203309**(43) Date of publication of application:  
**24.06.92 Bulletin 92/26**(84) Designated Contracting States:  
**AT BE CH DE DK ES FR GB GR IT LI LU MC  
NL SE**(71) Applicant: **AKZO N.V.**  
**Velperweg 76**  
**NL-6824 BM Arnhem(NL)**(72) Inventor: **Bergink, Engelbert Wilhelm**  
**Heischeutstraat 84**  
**NL-5345 VX Oss(NL)**(74) Representative: **Hermans, Franciscus G.M. et  
al**  
**P.O. Box 20**  
**NL-5340 BH Oss(NL)**(54) **Low estrogen oral contraceptives.**

(57) Disclosed is a contraceptive regimen, and method of using the regimen, comprising 24 daily sequential dosage units of: a first phase comprising about 7 to 9 separate first dosage units containing a progestogen at a daily dosage equivalent in progestogenic activity to 100 µg desogestrel and an estrogen at a daily dosage equivalent in estrogenic activity to 25 µg ethinyl estradiol ("EE"). A second phase of 7 to 9 second dosage units, each of the second dosage units containing a progestogen equivalent to 125 µg desogestrel and an estrogen equivalent to 20 µg EE. A third phase of 7 to 9 third dosage units, each unit containing a progestogen equivalent to 150 µg desogestrel and an estrogen equivalent to 20 µg EE. The kit generally has 28 daily dosage units wherein four of the daily dosage units contain no contraceptive steroid, or, alternatively, have only 24 dosage units with a four day "pill-free" period. The fourth phase may also be four dosage units containing a progestogen equivalent to 25 - 35 µg desogestrel.

**EP 0 491 415 A1**

Technical Field. The invention relates generally to oral contraceptive preparations, and more specifically to a low estrogen oral contraceptive regimen.

Background Art. Since the first birth control pill regimen was described, attempts have been made to lower the total steroid dosage in the regimen, while maintaining the regimen's reliability in providing contraception.

For example, U. S. Patent No. 4,628,051 to Ortho Pharm. Corp. discloses a three phase oral contraceptive containing estrogen and progestogen for administration over 21 days having a lower total monthly steroid dose having the same amount of estrogen in each phase. In the first phase, 5 to 8 tablets containing 0.02 to 0.05 milligrams (mg) ethinyl estradiol ("EE") and 0.065 to 0.75 mg of norethindrone ("NE") are administered daily. In the second phase, 7 to 11 tablets containing the same dosage of EE and 0.25 to 1 mg of NE are administered. In the third phase, 3 to 7 tablets containing the same dosage of EE and 0.35 to 2 mg of NE are administered. While an adequate contraceptive regimen, a 7 day pill free interval can lead to follicular development and thus pregnancy. Furthermore the preferred and described regimens administer 0.735 mg of EE, which to some is considered too large a dosage. Similar regimens are described in U.S. Patent Nos. 4,616,006, 4,544,554, and 4,530,839 also to Ortho Pharm. Corp.

West German patent application no. 3,341,638 to Hesslinger discloses another triphasic contraceptive regimen wherein contraceptive pills are administered over 22 days. The first phase of this regimen contains 6 pills having 30  $\mu$ g EE and 0.75 mg lynestrenol. The second phase contains 5 pills having 40  $\mu$ g EE and 1.0 mg lynestrenol. The third phase contains 11 pills having 30  $\mu$ g EE and 1.5 mg lynestrenol. This results in a total estrogen dose of 710  $\mu$ g of EE per cycle.

Another attempt to decrease estrogen levels in triphasic contraceptive regimens is described in Belgian patent 823,689 to Schering AG. In this contraceptive regimen of 21 pills, the first phase consists of 4 to 6 pills containing a first dose of estrogen (e.g. 30  $\mu$ g EE) and a first dose of progestogen (e.g. 50  $\mu$ g D-norgestrel). The second phase contains 4 to 6 pills containing one to two times the estrogen dose and one to one and a half times the progestogen dose of the first phase. The third phase contains 9 to 11 pills containing the same or a lesser amount of estrogen as the pills of the first phase, and up to three times the amount of progestogen. A very similar regimen is described in DE 3,347,125, also to Schering AG. Again, the 7 day pill free interval can lead to follicular development and thus pregnancy.

Another patent application of Schering AG (DT 2,645,307) describes a 28 day, 3 stage treatment for treating climacteric disorders. A 28 to 32 day steroid regimen, used in establishing cyclicity in human females, is disclosed in U.S. Patent No. 3,639,600 to Upjohn wherein 2.550 mg of EE is administered over the treatment period.

DT 2,431,704 to Asche CF & Co. AG discloses a triphasic contraceptive where, in the first stage, a low dose of estrogen (e.g. 0.030 mg EE) and a progestogen (e.g. 1.00 mg norethisterone acetate) are administered for 6 to 8 days; in the second stage, a slightly increased ( $\leq$  2-fold) dose of estrogen and slightly increased ( $\leq$  1.5-fold) dose of progestogen are administered for 6 to 8 days; and, in the third stage, an estrogen dose no higher than the second stage, and an increased ( $\leq$  3-fold of the first stage) progestogen dose are administered for 6 to 8 days. At the very least, 630  $\mu$ g of EE is still administered in this particular regimen.

South African patent 8509-892-A to Warner Lambert Co. describes a three or four phase oral contraceptive regimen having a relatively high amount of norethindrone acetate (i.e. from 0.5 to 1.5 mg) and relatively low amount of EE (10 to 50  $\mu$ g) or other estrogenic substance. The four phase regimen is administered over a 23 to 34 day cycle having an inactive phase.

European Patent application 253,607 to American Home Prods. discloses a mono-phasic contraceptive preparation containing 23 to 25 dosage units having 0.008 to 0.030 mg of EE in combination with 0.025 to 0.100 mg of desogestrel which is administered over 23 to 25, preferably 24, days followed by a 2 to 5 day pill-free period.

Still another attempt to minimize estrogen levels in sequential oral contraceptives is disclosed in Dutch patent application 6911920 to Unisearch Ltd. This patent application describes a pack containing at least 28 pills, 25 to 27 of which are active. Of the active pills, 17 to 20 are estrogen only (e.g. ethinyl estradiol) pills, with the remainder containing both an estrogen and a progestogen. The low estrogen pills contain 0.050 to 0.080 mg of an estrogen, while the high estrogen pills contain 0.07 to 0.08 mg estrogen. The combination pills contain 0.07 to 0.12 mg estrogen and 0.8 to 1.4 mg of progestogen. Even with this minimized estrogen contraceptive, at least 1.610 mg of estrogen are administered, while in the preferred embodiment, 1.950 mg are administered.

European patent application no. 36,229 to Akzo, nv discloses a multiphase combination-type sequential oral contraceptive consisting of 20 to 22 tablets each containing a progestogen and an estrogen. The first phase contains a relatively low dose of progestogen (e.g. less than 50 micrograms of desogestrel), followed

by phases containing more progestogen (e.g. 100 µg and 200 µg desogestrel in the second and third phases, respectively).

A need exists for an effective low dose contraceptive regimen having the benefits of multi-phasic administration (e.g. ideal cycle control), while still preventing follicular development during the pill-free interval.

#### Disclosure of the Invention

It has been found that by properly selecting, at a low level, the dosage of the estrogen component in a multi-phasic contraceptive regimen, and administering it over 24 days, while at the same time slowly and incrementally increasing the progestogen administered, a highly reliable contraceptive regimen having low doses of both estrogen and progestogen is attained.

The invention thus includes a multiphasic combination and contraceptive kit containing at least three phases. These three phases consist of 24 daily sequential daily dosage units, i. e. a first phase having 7 to 9 separate first dosage units, the first dosage units containing a progestogen at a daily dosage equivalent in progestogenic activity to 75 to 100 micrograms desogestrel and an estrogen at a daily dosage equivalent in estrogenic activity to 25 micrograms ethinyl estradiol. The second phase has 7 to 9 second dosage units, each of the second dosage units containing a progestogen at a daily dosage equivalent in progestogenic activity to 100 to 125 micrograms desogestrel and an estrogen at a daily dosage equivalent in estrogenic activity to 20 micrograms ethinyl estradiol. The third phase has 7 to 9 third dosage units, each of the third dosage units containing a progestogen at a daily dosage equivalent in progestogenic activity to 125 to 150 micrograms desogestrel and an estrogen at a daily dosage equivalent in estrogenic activity to 20 micrograms ethinyl estradiol.

The kit will generally have 28 daily dosage units (i.e. include a fourth phase) wherein four of the daily dosage units contain no contraceptive steroid (e.g. are "blanks" or placebos or contain iron). Alternatively a four day "pill-free" period may be utilized, or the fourth phase may also be four daily dosage units containing a progestogen at a daily dosage equivalent in progestogenic activity to 25 to 35 micrograms desogestrel.

The invention also includes a contraceptive product (i.e. the birth control pack containing the dosage unit regimen), and a process of manufacturing this product.

#### Best Mode of the Invention

Preferred progestogens for use with the invention include 3-ketodesogestrel ("etonogestrel"), desogestrel, levo-norgestrel, norgestrel, gestodene, and other compounds with similar progestogenic activity. Especially preferred are 3-ketodesogestrel and desogestrel. As an approximation, levo-norgestrel, desogestrel, and 3-keto-desogestrel are relatively equipotent in progestogenic activity. Gestodene is approximately 1.5 times as potent as these compounds. Norgestrel is about one-half as potent as levo-norgestrel.

Examples of preferred estrogens include 17β-estradiol and ethinyl estradiol. Mestranol and 17-α-ethinyl estradiol 3-methylether are also useful estrogens. As an approximation, 1 mg of 17β-estradiol is equivalent in estrogenic activity to 0.015 mg of ethinyl estradiol and 0.030 mg of mestranol.

The estrogen and progestogen ("contraceptive steroids"), or either of them are incorporated into dosage units for oral administration. The term "dosage unit" generally refers to physically discrete units suitable as unitary dosages for humans or animals, each containing a predetermined quantity of active material (e.g. estrogen or progestogen) calculated to produce the desired effect.

Methods and compositions for making such dosage units are well-known to those skilled in the art. For example, methods and compositions for making tablets and pills, containing active ingredients, are described in the standard reference, Chase et al., *Remington's Pharmaceutical Sciences*, (16th ed., Mack Publishing Co., Easton, PA, U.S.A., 1980) ("Remington's"), at pages 1553 to 1584. Methods of making powders, and their composition are described at pages 1535 to 1552 of the reference. Methods of coating pharmaceutical dosage forms are described at pages 1585 to 1593 of *Remington's*.

For making dosage units, e.g. tablets, the use of conventional additives, e.g. fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used in the one or more of the compositions.

Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like used in suitable amounts. Lactose is a preferred carrier. Mixtures of carriers can also be used.

A process of manufacturing the combination and contraceptive kit involves mixing predetermined

quantities of progestogen with predetermined quantities of estrogen and converting the mixture into the first dosage units (e.g. by filling capsules or molding tablets with the mixture and any desired excipients); mixing predetermined quantities of progestogen with predetermined quantities of estrogen and converting that mixture into the second dosage units; and mixing predetermined quantities of progestogen with predetermined quantities of estrogen and converting that mixture into the third dosage units.

A preferred process of manufacturing the contraceptive product according to the invention involves incorporating the desired dosages of contraceptive steroid (i.e. progestogen with or without estrogen) into a tablet by known techniques. Tablets containing different amounts and types of contraceptive steroids may be of different colors, and kept in different portions of, for example, a blister pack. The package containing the dosage units will preferably contain 24 to 28 dosage units arranged sequentially therein. Preferably there will be 28 dosage units.

A preferred method of contraception using the invention comprises administering to a pre-menopausal fertile female:

for the first 7 to 9 days, separate first dosage units containing a progestogen at a daily dosage equivalent in progestogenic activity to 100 micrograms desogestrel and an estrogen at a daily dosage equivalent in estrogenic activity to 25 micrograms ethinyl estradiol;

for the next 7 to 9 days, second dosage units each containing a progestogen at a daily dosage equivalent in progestogenic activity to 125 micrograms desogestrel and an estrogen at a daily dosage equivalent in estrogenic activity to 20 micrograms ethinyl estradiol;

for the next 7 to 9 days, third dosage units, each containing a progestogen at a daily dosage equivalent in progestogenic activity to 150 micrograms desogestrel and an estrogen at a daily dosage equivalent in estrogenic activity to 20 micrograms ethinyl estradiol; and

for the next 4 days and to complete the regimen, either a "pill-free" period, dosage units containing no contraceptive steroid, or dosage units containing a progestogen at a daily dosage equivalent in progestogenic activity to 25 to 35 micrograms desogestrel. The first, second, and third dosage units are administered for a total of 24 days. After the completion of a regimen, the regimen is repeated for as long as contraception is desired. One or more dosage units may contain an iron salt (e.g. 75 mg of ferrous fumarate) if desired.

A preferred regimen is administered to a female of child bearing age at the following times over a 28 day period:

(a) for 8 days a composition containing 25 µg ethinyl estradiol and 100 µg desogestrel or equivalent amount of other progestogen;

(b) for 8 days a composition containing 20 µg ethinyl estradiol and 125 µg desogestrel or equivalent amount of other progestogen;

(c) for 8 days a composition containing 20 µg ethinyl estradiol and 150 µg desogestrel or equivalent amount of other progestogen; and

(d) for 4 days a composition containing 25 to 35 µg desogestrel or equivalent amount of other progestogen.

The invention is further explained by the following illustrative EXAMPLES.

#### EXAMPLE I

Compositions of tablets:

A. In the first phase: (8 tablets)

Compound	Amount (mg/tablet)
ethinyl estradiol	0.025
desogestrel	0.100
potato starch	8.000
polyvinyl pyrrolidone	2.400
stearic acid	0.800
silica	0.800
dl-α-tocopherol	0.080
lactose	qsad 80.000

B. In the second phase: (8 tablets)

Compound	Amount (mg/tablet)
ethinyl estradiol	0.020
desogestrel	0.125
potato starch	8.000
polyvinyl pyrrolidone	2.400
stearic acid	0.800
silica	0.800
dl- $\alpha$ -tocopherol	0.080
lactose	qsad 80.000

C. In the third phase: (8 tablets)

Compound	Amount (mg/tablet)
ethinyl estradiol	0.020
desogestrel	0.150
potato starch	8.000
polyvinyl pyrrolidone	2.400
stearic acid	0.800
silica	0.800
dl- $\alpha$ -tocopherol	0.080
lactose	qsad 80.000

D. In the fourth phase: (4 tablets)

Compound	Amount (mg/tablet)
desogestrel	0.030
potato starch	8.000
polyvinyl pyrrolidone	2.400
stearic acid	0.800
silica	0.800
dl- $\alpha$ -tocopherol	0.080
lactose	qsad 80.000

## EXAMPLE II

The same as in EXAMPLE I, except that the fourth phase is substituted with tablets having no steroid.

## EXAMPLE III

Compositions of tablets:

A. In the first phase: (8 tablets)

EP 0 491 415 A1

Compound	Amount (mg/tablet)
ethinyl estradiol	0.025
3-ketodesogestrel	0.100
potato starch	8.000
polyvinyl pyrrolidone	2.400
stearic acid	0.800
silica	0.800
dl- $\alpha$ -tocopherol	0.080
lactose	qsad 80.000

B. In the second phase: (8 tablets)

Compound	Amount (mg/tablet)
ethinyl estradiol	0.020
3-ketodesogestrel	0.125
potato starch	8.000
polyvinyl pyrrolidone	2.400
stearic acid	0.800
silica	0.800
dl- $\alpha$ -tocopherol	0.080
lactose	qsad 80.000

C. In the third phase: (8 tablets)

Compound	Amount (mg/tablet)
ethinyl estradiol	0.020
3-ketodesogestrel	0.150
potato starch	8.000
polyvinyl pyrrolidone	2.400
stearic acid	0.800
silica	0.800
dl- $\alpha$ -tocopherol	0.080
lactose	qsad 80.000

D. In the fourth phase: (4 tablets)

Compound	Amount (mg/tablet)
3-ketodesogestrel	0.030
potato starch	8.000
polyvinyl pyrrolidone	2.400
stearic acid	0.800
silica	0.800
di- $\alpha$ -tocopherol	0.080
lactose	qsad 80.000

## EXAMPLE IV

The same as in EXAMPLE III, except that the fourth phase is substituted with tablets having no steroid.

## 5 EXAMPLE V

Compositions of tablets:

A. In the first phase: (8 tablets)

10

Compound	Amount (mg/tablet)
micronized estradiol	3.000
3-ketodesogestrel	0.100
potato starch	8.000
polyvinyl pyrrolidone	2.400
stearic acid	0.800
silica	0.800
dl- $\alpha$ -tocopherol	0.080
lactose	qsad 80.000

15

20

B. In the second phase: (8 tablets)

25

Compound	Amount (mg/tablet)
micronized estradiol	2.000
3-ketodesogestrel	0.125
potato starch	8.000
polyvinyl pyrrolidone	2.400
stearic acid	0.800
silica	0.800
dl- $\alpha$ -tocopherol	0.080
lactose	qsad 80.000

30

35

C. In the third phase: (8 tablets)

40

Compound	Amount (mg/tablet)
micronized estradiol	2.000
3-ketodesogestrel	0.150
potato starch	8.000
polyvinyl pyrrolidone	2.400
stearic acid	0.800
silica	0.800
dl- $\alpha$ -tocopherol	0.080
lactose	qsad 80.000

45

50

D. In the fourth phase: (4 tablets)

55

EP 0 491 415 A1

Compound	Amount (mg/tablet)
3-ketodesogestrel	0.030
potato starch	8.000
polyvinyl pyrrolidone	2.400
stearic acid	0.800
silica	0.800
dl- $\alpha$ -tocopherol	0.080
lactose	qsad 80.000

EXAMPLE VI

The same as in EXAMPLE V, except that the fourth phase is substituted with tablets having no contraceptive steroid.

EXAMPLE VII

Compositions of tablets:

A. In the first phase: (8 tablets)

Compound	Amount (mg/tablet)
ethinyl estradiol	0.025
desogestrel	0.075
potato starch	8.000
polyvinyl pyrrolidone	2.400
stearic acid	0.800
silica	0.800
dl- $\alpha$ -tocopherol	0.080
lactose	qsad 80.000

B. In the second phase: (8 tablets)

Compound	Amount (mg/tablet)
ethinyl estradiol	0.020
desogestrel	0.125
potato starch	8.000
polyvinyl pyrrolidone	2.400
stearic acid	0.800
silica	0.800
dl- $\alpha$ -tocopherol	0.080
lactose	qsad 80.000

C. In the third phase: (8 tablets)



Compound	Amount (mg/tablet)
ethinyl estradiol	0.020
desogestrel	0.150
potato starch	8.000
polyvinyl pyrrolidone	2.400
stearic acid	0.800
silica	0.800
dl- $\alpha$ -tocopherol	0.080
lactose	qsad 80.000

D. In the fourth phase: (4 tablets)

Compound	Amount (mg/tablet)
potato starch	8.000
polyvinyl pyrrolidone	2.400
stearic acid	0.800
silica	0.800
dl- $\alpha$ -tocopherol	0.080
lactose	qsad 80.000

### Claims

1. A multiphasic combination and contraceptive kit comprising three phases, said three phases consisting of 24 daily sequential dosage units with:
  - a first phase comprising from 7 to 9 separate first dosage units, said first dosage units containing a progestogen at a dosage equivalent in progestogenic activity to 75 - 100  $\mu$ g desogestrel and an estrogen at a dosage equivalent in estrogenic activity to 25  $\mu$ g ethinyl estradiol;
  - a second phase of 7 to 9 second dosage units, each said second dosage unit containing a progestogen at a dosage equivalent in progestogenic activity to 100 - 125  $\mu$ g desogestrel and an estrogen at a dosage equivalent in estrogenic activity to 20  $\mu$ g ethinyl estradiol; and
  - a third phase of 7 to 9 third dosage units, each said third dosage units containing a progestogen at a dosage equivalent in progestogenic activity to 125 - 150  $\mu$ g desogestrel and an estrogen at a dosage equivalent in estrogenic activity to 20  $\mu$ g ethinyl estradiol.
2. The multiphasic combination and contraceptive kit of claim 1 further comprising a fourth phase comprising 4 more dosage units containing no contraceptive steroid.
3. The multiphasic combination and contraceptive kit of claim 1 further comprising a fourth phase comprising 4 more dosage units containing a progestogen at a dosage equivalent in progestogenic activity to 25 to 35  $\mu$ g desogestrel.
4. The multiphasic combination and contraceptive kit of claim 1, claim 2 or claim 3 wherein said progestogen is selected from the group consisting of desogestrel, 3-ketodesogestrel, levo-norgestrel, gestodene, and mixtures thereof.
5. The multiphasic combination and contraceptive kit of claim 4 wherein said progestogen is desogestrel or 3-ketodesogestrel.
6. The multiphasic combination and contraceptive kit of claim 5 wherein said progestogen is present in a quantity per dosage unit of 100  $\mu$ g in the first dosage units, 125  $\mu$ g in the second dosage units, and 150  $\mu$ g in the third dosage units.

7. The multiphasic combination and contraceptive kit of any of claims 1 to 6 wherein said estrogen is selected from the group consisting of  $17\beta$ -estradiol, ethinyl estradiol, mestranol,  $17\alpha$ -ethinyl estradiol 3-methylether, and mixtures thereof.
- 5 8. The multiphasic combination and contraceptive kit of claim 7 wherein said estrogen is  $17\beta$ -estradiol or ethinyl estradiol.
9. A process of manufacturing the combination and contraceptive kit of claim 1 comprising:
  - 10 mixing predetermined quantities of progestogen with predetermined quantities of estrogen and converting said mixture into said first dosage units;
  - mixing predetermined quantities of progestogen with predetermined quantities of estrogen and converting said mixture into said second dosage units; and
  - mixing predetermined quantities of progestogen with predetermined quantities of estrogen and converting said mixture into said third dosage units.
- 15 10. A method of contraception in a female comprising orally administering in 28 day cycles to a premenopausal fertile female, for so long as contraception is desired, the following:
  - for a first 7 to 9 days, separate first dosage units containing a progestogen at a daily dosage equivalent in progestogenic activity to 75-100  $\mu$ g desogestrel and an estrogen at a daily dosage
  - 20 equivalent in estrogenic activity to 25  $\mu$ g ethinyl estradiol;
  - for the next 7 to 9 days, second dosage units each second dosage unit containing a progestogen at a daily dosage equivalent in progestogenic activity to 101-125  $\mu$ g desogestrel and an estrogen at a daily dosage equivalent in estrogenic activity to 20  $\mu$ g ethinyl estradiol;
  - for the next 7 to 9 days, third dosage units, each third dosage unit containing a progestogen at a
  - 25 daily dosage equivalent in progestogenic activity to 126-150  $\mu$ g desogestrel and an estrogen at a daily dosage equivalent in estrogenic activity to 20  $\mu$ g ethinyl estradiol; and
  - for the last 4 days of said 28 days, either administering nothing or blank dosage units or dosage units consisting essentially of a progestogen at a daily dosage equivalent in progestogenic activity to 25-35  $\mu$ g desogestrel.



European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number

EP 91 20 3182

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y,D	EP-A-0 036 229 (AKZO N.V.) * Pages 1-3; claims 1-14 * ---	1-10	A 61 K 31/565
Y,D	EP-A-0 253 607 (AMERICAN HOME PRODUCTS CORP.) * Column 9, line 7 - column 11, line 13; claims 1-17 * ---	1-10	
A,D	DE-A-2 431 704 (ASCHE AG) -----	1-10	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			A 61 K
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 26-03-1992	Examiner LEHERTE C.F.M.
<b>CATEGORY OF CITED DOCUMENTS</b> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ..... & : member of the same patent family, corresponding document			

EPO FORM 1501.03.82 (P0401)

THIS PAGE BLANK (USPTO)